

THE WILLIAM HENRY WELCH LECTURES

I. SOME NEW ASPECTS OF HOMEOSTASIS

BY

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Reprinted from JOURNAL OF THE MOUNT SINAI HOSPITAL
VOL. V, NO. 5, JANUARY-FEBRUARY, 1939

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THE WILLIAM HENRY WELCH LECTURES

I. SOME NEW ASPECTS OF HOMEOSTASIS¹

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Our bodies are composed of extraordinarily unstable material. Muscles are made to contract by almost incredibly minute nerve impulses; it has been estimated that the energy of a single impulse is related to the energy of the consequent muscular twitch as 1/200,000. The olfactory surface has long been known to be marvelously sensitive; by means of it we can perceive the presence of mercaptan in a dilution of 1/23,000,000 of a milligram diffused in a liter of air. And the retina is reported to be three thousand times more delicately responsive than the most sensitive photographic plate. Further evidence of the instability of living structure is found in the common experience of fainting. Even a slight check of the blood supply to some nerve cells of the brain abolishes consciousness, and total anemia for eight or nine minutes may result in irreparable injury of such cells.

When we consider the extreme instability of parts of our body structure, their readiness for disturbance when only slight external forces are applied, and their rapid deterioration in the absence of favoring conditions, the persistence of the normal state and normal activity through many decades seems nothing short of miraculous.

When we consider further that our organisms form an open system, engaging in a free exchange of material with the outer world, and that the bodily structure itself is not permanent but is being continuously broken down with every action and continuously built up by the process of repair, the wonder of persistent normality and function increases.

The ability of higher organisms to maintain a fairly constant state has long impressed biologists. The idea that corrective agencies are present in living beings is at least 2,300 years old. Centuries ago that idea was expressed in the phrase, "*vis medicatrix naturae*"—the recognition of a factor or factors restoring the normal state when that has been disturbed. In recent times eminent physiologists—Richet, Pflüger and Fredericq—have emphasized this remarkable phenomenon. Indeed, Fredericq (1) declared that the higher the position of an organism in

¹ Delivered at The Blumenthal Auditorium, The Mount Sinai Hospital, New York City, May 18, 1938.

the scale of living beings the more numerous, the more perfect, and the more complicated are the corrective agencies.

An important contribution toward understanding the phenomenon of organic stability was offered by Claude Bernard (2) about ninety years ago. He pointed out that, as living beings, we have not only the same external environment as other objects but also an "internal environment." In a sense we are not air-inhabiting animals, for we are separated from the surrounding air by a layer of dead stuff, the horny scurf of the skin and the moisture of the mucous membranes. All that is alive within these lifeless coverings is in contact with fluid. Indeed, our living parts may be conceived as bathed by a watery solution of salts and colloids—the blood, the lymph, and tissue fluids. It is these fluids which form a *milieu interne*, as Claude Bernard expressed it, or a fluid matrix, as I prefer to call it.

Just in so far as the internal environment, or fluid matrix, is kept constant are we independent of limiting changes in the external environment; we carry with us always our own personal atmosphere. Also we are independent of the disturbances of the internal environment that are produced by our own actions. The freedom which is thus assured is a privilege of the higher vertebrates, birds and mammals. We have evidence that in the process of evolution the devices assuring a constant state were only gradually achieved. For example, the frog, in which control of body water and temperature is lacking, is limited in the summer to the vicinity of a moist region and in the winter must sink to the bottom of a frigid pool; only when the warmth of spring returns is he freed from the paralyzing effects of the icy water. Birds, on the contrary, with their feathery covering, may spend the winter in vigorous activity because of special devices for keeping warm.

The constancy of the fluid matrix is controlled by the organism itself. In that control many complex physiological processes may be involved. The term "equilibrium," which is technically applied to simple physical and chemical systems, is not adequate to express the complicated arrangements in the body for preserving uniformity. I have suggested, therefore, that the relatively stable state maintained in the fluid matrix should be given the special name, "homeostasis" (3).

During the past nine years investigators in the Harvard Physiological Laboratory have presented evidence that the sympathetic division of the autonomic nervous system plays an important rôle in controlling the homeostatic devices of the body. Almost all the studies, however, were made on cats. Recently our evidence has been questioned, mainly by C. Heymans (4) and his collaborators, because of effects which they have observed on sympathectomized dogs. Whereas the sympathectomized cat, when exposed to exacting conditions, showed notable deficiencies, the sympathectomized dog exposed to similar conditions was hardly

distinguishable from the normal dog. The cat and the dog differ, however, in their natural habits, one being relatively sedentary, the other remarkably active. In the present lecture I propose to compare these two as animal types, when normal and when deprived of the sympathetic nerve supply, and incidentally to review the evidence for homeostatic control of the fluid matrix. Also I propose to consider an extension of the concept of homeostasis.

As an introduction to the facts which will be presented, may I remind you that the sympathetic division of the autonomic nervous system is connected with the central nervous axis between the brachial and the sacral enlargements of the spinal cord, and that it consists mainly of two ganglionic chains reaching from high in the neck to the pelvis, one on each side of the midline, close to the spinal column. From these ganglia postganglionic fibers pass out to the smooth muscles of blood vessels and hairs, to sweat glands and to other glands (including the adrenal medulla), and also to the heart. It is quite possible to remove the ganglionic chains in whole or in part. When a cat, for example, is thus operated upon it continues its existence indefinitely in the confines of the laboratory where food is provided, temperature is regulated, and the struggle for existence is minimal. Deficiencies appear only when the constancy of the fluid matrix is in danger. These deficiencies are various. At present I propose to consider those that become manifest upon exposure to heat and cold, to the possibilities of insufficient oxygen, and to a low concentration of blood sugar.

Exposure to Cold. When the sympathectomized cat is placed in a cold environment the hairs do not rise and enmesh a layer of protective air around the body. Furthermore, there is no narrowing of the surface blood vessels to check the distribution of warm blood to the cold skin. Still another defect is the failure of secretion of adrenine from the adrenal medulla. A small amount of this remarkable substance, one milligram, injected subcutaneously, will accelerate the metabolic processes of the body, as shown by Boothby and Sandiford (5), to the extent of producing fifty extra calories. Without the sympathetic the advantage of this extra heat production is lost. In such circumstances, sympathectomized cats left in an environment of approximately 5°C., are demonstrably less able than normal cats to maintain the ordinary level of body temperature. Their temperature may drop as much as 2.5°C. within two hours, in spite of vigorous shivering. The shivering, of course, produces extra heat in the body but by itself it is usually ineffective in preserving temperature homeostasis.

When Heymans and his collaborators reported that there was no noteworthy deficiency of sympathectomized dogs if exposed to cold, they based the statement on incidental observations. They did not record careful attention to the temperature of the air nor to the temperature of the dogs.

In recent studies in the Harvard Laboratory, carried on by Dr. McDonough (6), dogs of similar hair coat and size were compared, as normal and as sympathectomized animals. They were exposed to temperatures of approximately 5°C. Under these conditions, not only the sympathectomized but also the normal dogs shivered vigorously (normal cats rarely shiver at 5°). Records of shivering revealed that in the normal animals the rate was in the neighborhood of 400 muscular contractions per minute. In the sympathectomized dogs it was approximately 50 per cent higher. Despite the higher rate, however, there was a fall of body temperature in the sympathectomized animals. It was not so great a fall as was observed in cats deprived of the sympathetic system, being only about 0.5°C., but it was typically present. From these observations we may conclude that because of its service in lifting the hair, in contracting surface vessels and discharging adrenine, the sympathetic system is useful to dogs as it is to cats in maintaining a stable state. When the system is absent the animals resort to shivering sooner and more vigorously than do normal animals. The dog, however, differing from the cat in being much more muscular, produces more heat in shivering. Furthermore, even in his normal state he is accustomed to shivering as a means of maintaining a homeostasis of temperature. For these two reasons we can explain the greater effectiveness of the dog as compared with the cat in a cold environment after the sympathetic system has been removed.

Exposure to Heat. When warm-blooded animals, having sudorific glands, are exposed to a high temperature, homeostasis is preserved by the secretion of sweat which, on evaporating, cools the skin, and also by superficial vasodilation which allows the warm blood to lose heat to the cool skin. Both sweating and dilation of the blood vessels are under control of the sympathetic system. Also panting may be used, which provides an evaporation from the upper respiratory passages and thereby a cooling of the fluid matrix, as represented in the flowing blood. Panting is made especially effective, of course, by evaporation of saliva.

When sympathectomized cats are exposed to a warm atmosphere sweating is impossible. There is a possibility of vasodilation in these animals, but whether it occurs is undetermined. In cats, panting is a rare mode of regulating body temperature. When, therefore, sympathectomized cats are placed in warm surroundings (about 40°C.) they are readily shown to have a defective temperature control. The temperature may rise a full degree (C.) higher in these animals than in normal cats in the same circumstances (7).

When sympathectomized dogs are compared with normal dogs having similar hair coats and undergoing exposure to the same moderate heat for the same length of time, the body temperature may indeed rise somewhat higher in the animals operated upon than in the normal. The increase, however, is negligible. Again the dog is revealed as an extraordinarily

efficient organism despite the absence of the sympathetic system. This superiority of the sympathectomized dog as compared to the sympathectomized cat when in a warm environment is explained by the remarkable accessory devices possessed by the dog in his great tongue and lavish discharge of saliva. The dog promptly resorts to panting when his temperature tends to rise. By the evaporation of saliva (a parasympathetically controlled secretion not interfered with by sympathectomy) heat is removed from the tongue and mouth where the blood abundantly circulates. Thus the body temperature is kept from rising. This striking accessory mode of avoiding a rise of body temperature is associated with the greater activity of the dog as compared with the cat. The dog is characteristically an active animal, running uninterruptedly for long distances and producing through muscular exertion a large amount of heat. The cat is typically a quiet animal, capable only of quick, short spurts of running. Since the dog has sweat glands only on the nose and toe pads, panting and a great outflow of saliva for evaporation become the chief means of heat loss—a means which is rarely employed by the cat.

The Acid-base Balance. The fact is familiar that the reaction of the blood is slightly alkaline—whereas a pH of 7 is neutral, the blood on the alkaline side of neutrality is expressed by a pH of 7.4. Close to that figure it is ordinarily held by the homeostatic factors; it may become further alkaline, to 7.8, whereupon convulsions may occur, or it may be reduced very slightly below 7.0, whereupon coma supervenes. In vigorous muscular work a large amount of non-volatile lactic acid is produced, an amount which would soon overwhelm the alkaline buffer in the blood. The danger of coma which might result is avoided by a supply of extra oxygen to the active tissues, where the lactic acid may be burned to volatile carbonic acid and then breathed away through the lungs. In the process of supplying the extra oxygen the organs controlled by the sympathetic system come into service. The heart is made to beat more rapidly, the blood pressure rises, and by contraction of the spleen extra erythrocytes are pressed into use in the circulation. With a higher head of arterial pressure the rate of blood flow between the lungs and active organs is increased. By this faster flow and the greater number of red corpuscles in the circulating stream the delivery of oxygen is greatly augmented. Associated with these changes, brought about through sympathetic control, there is an increase of respiration. This assures a larger supply of oxygen in the lungs and a more rapid removal of carbon dioxide from them.

When the sympathectomized cat engages in even moderate muscular activity it is instantly revealed as a very defective animal. The arterial pressure, instead of rising, actually falls, and if the cat attempts to run it is likely to faint (8). It is therefore incapable of prolonged or vigorous action. The fall of pressure is due to vasodilator impulses carried to the arterioles over non-sympathetic pathways. When the depressor points

in possessing excellent homeostatic functions. Doubtless a man would suffer more from removal of the sympathetic system than does the dog, because he depends on sweating for temperature control when excessive heat is produced by muscular exertion or when he is exposed to high external heat. He does not ordinarily make use of panting. Since sweating is under sympathetic control, man would obviously be at a definite disadvantage compared with the dog in the critical state of a rising body temperature.

There are, to be sure, bodily conditions in which the special provisions which the dog enjoys as a running animal cannot compensate in maintaining homeostasis. One of these is seen in the general response of organisms to the hypoglycemia produced by insulin. Normally, secretion from the adrenal medulla is pre-eminently the agent for liberating glucose from the liver (17). If the adrenal glands are intact and receiving sympathetic impulses, and insulin is given in such a dose as to cause the blood sugar to fall, at a critical point in the fall the sympathetic system will be brought into action (18). Adrenine will be secreted into the blood stream—as disclosed by the faster beat of the denervated heart—and the drop in blood sugar will be checked. The injection of glucose into the blood stream will promptly stop the extra discharge of adrenine from the adrenal medulla. If the adrenal glands, however, are no longer under nervous control, as in the sympathectomized animal, the same test will result in a progressive hypoglycemia—there will be no adrenal secretion, as shown by failure of acceleration of the denervated heart, and the drop in the glucose concentration of the blood will not be checked.

When normal cats are subjected to a standard dose of insulin (0.5 unit per kilogram) there is commonly no reduction of blood sugar to the convulsive level, and if it is reduced to that level, the effect is belated. In sympathectomized cats, on the contrary, the same dose produces convulsions in some instances, or, if not convulsions, very serious conditions from which the animals must be rescued by glucose injections (19). The same phenomena are observed in contrasting normal and sympathectomized dogs. A dose of insulin (0.5 unit per kilogram) which does not produce convulsions in the normal animals results in convulsions or collapse in the sympathectomized, from which they must be rescued by receiving glucose (6). In these circumstances it is obvious that the sympathetic system as a homeostatic regulator is quite as important in the dog as it is in the cat.

Now I wish to consider with you an extension of the concept of homeostasis. Originally the idea was associated with constancy of the fluid matrix as a whole, that is, to the relatively uniform state of the blood and lymph throughout the body. The value of this uniformity of the *milieu interne* was conceived by Bernard, Fredericq and Richet, as resulting from stable states throughout the organism. We must recognize, however.

that there are provisions for preserving constancy of local conditions in the body. A few examples will make the meaning clear.

When muscles become active, as Krogh (20) has shown, many capillaries which are collapsed during muscular rest are opened and serve as effective carriers of oxygen; they may be from forty to one hundred times as numerous in the contracting as in the resting muscle. Observations have shown that the blood flow may be five times as great through the active muscle as it is through the inactive. This especially faster flow in a region of high metabolism supplies the extra oxygen and the energy-yielding material required for the more vigorous chemical processes which are taking place. Furthermore, the faster flow more effectively carries away the extra waste materials which result from the chemical processes. In times of need, therefore, there are arrangements for local homeostasis, i.e., for local preservation of uniform conditions (16).

Another illustration is found in the blood supply of certain endocrine glands. These glands secrete substances which might be highly concentrated at the source unless there were special devices for dilution. Unfortunately we do not know about the blood flow in many of the endocrine organs. We have information, however, concerning the thyroid and the adrenals. The circulation in these glands, when calculated for standard conditions and for unit weight of the organs, is revealed as many times that of other organs (21). Again we note an arrangement for local homeostasis.

There are also special provisions for essential and peculiarly sensitive structures. Notable among them are the very delicate neurones of the cerebral cortex and the muscle of the continuously active heart. Unless a sufficiently high arterial pressure is present the delivery of oxygen to the organs of the body will be inadequate. In a falling blood pressure a critical level is reached at approximately 70 mm. of mercury. Below this level the alkaline buffers of the blood begin to be neutralized by non-volatile acid, as revealed by reduction of the carbon-dioxide capacity, and also by decrease of the metabolic rate (22). Associated with this evidence of a critical level are observations showing that the heart and parts of the brain are progressively damaged as the pressure is reduced and persists below that level.

If a hemorrhage is produced—for example, 15 or 20 per cent of the estimated blood volume—there is a sharp fall of blood pressure. Only a few minutes elapse, however, until the pressure is restored to approximately the former height. Thus a proper supply of blood is assured to the brain and to the heart. This remarkable and prompt adjustment of the circulation is a function of the sympatho-adrenal system, for in sympathectomized animals the rise after such hemorrhage does not occur (23). It results from proprioceptive reflexes, from the carotid sinus, and from the arch of the aorta, which operate in such fashion that the

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blood vessels generally throughout the body, except in the heart and the brain, are contracted so that the capacity of the vascular system fits the reduced volume of blood and therefore maintains in these essential and most sensitive organs an adequate supply of oxygen.

We must conceive homeostasis, therefore, as involving not only the state of relative uniformity of the fluid matrix throughout the organism but also a local and specialized condition as manifest in active parts—muscles, for example—and in endocrine glands. Moreover, we must conceive the homeostatic mechanisms as being operated in such manner as to provide for preferential treatment of primarily important structures. Thus, in case of hemorrhage or the first stages of shock, a constant state is assured for the heart and the brain. This preferential treatment is obtained, to be sure, at the expense of other organs, organs in which the blood vessels are constricted and in which, therefore, the blood supply is temporarily reduced. Supporting the devices which provide local homeostasis there are the widely influential and well-recognized mechanisms. Thus, in vigorous exertion, when the laboring muscles are benefiting from local changes in the circulation, the heart, the blood vessels, the spleen, and the lungs are collaborating. By that collaboration they send to the muscles which are engaged in action a more abundant supply of oxygen and the material for effective performance, and they prevent in the organism as a whole an accumulation of waste arising therefrom. Also, after hemorrhage there is an inflow of fluid from the tissue spaces which increases the volume of the circulating blood. As this occurs there is gradual relaxation of the constricted blood vessels, and consequently a proper flow of blood to the organs which temporarily have surrendered their quota to the heart and brain.

Such are some of the newer aspects of homeostasis to which I call your attention. There has been no essential criticism hostile to the concept of homeostasis and no evidence which indicates that the sympathetic system does not play an important rôle in homeostatic regulation. Finally, there is recognition of the fact that we need much more information than we now have in order to understand more thoroughly the nice devices in the organism for maintaining its stability.

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